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Severe Acute Respiratory Distress Syndrome

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Abstract

Acute respiratory distress syndrome is characterized by an increase of the permeability of the lungs' alveolar-capillary membranes, leading to the extravasation of liquid rich in proteins inside the alveolar spaces that turns air-filled lungs into heavy high-osmotic pressure liquid-filled lungs. The consequence is the collapse of the lowermost lung regions, shunt, refractory hypoxemia, decrease in lungs' compliance and increase in dead spaces that are more pronounced with the severity of the permeability changes of the pulmonary alveoli-capillary membrane. According to the recent Berlin definition, severe acute respiratory distress syndrome is defined by bilateral pulmonary infiltrates of recent onset (less than 1 week) in a patient with a risk factor for ARDS that has a $\text{PaO}_2/\text{FIO}_2$ equal or less than 100 with a positive end-expiratory pressure equal or more than 5 cm H_2O with no evidence of cardiac failure or hypervolemia. Severe ARDS patients present a higher mortality ratio, a more difficult mechanical ventilatory support (higher airway pressures with low tidal ventilation and higher PaCO_2 levels) and benefits for adjunctive ventilatory support therapy. The recommended mechanical ventilatory support in severe ARDS is with low tidal ventilation (less than 6 mL/Kg predicted body weight) with driving inspiratory pressures less than 15 cm H_2O , respiratory rate sufficient to keep adequate minute ventilation and PaCO_2 levels. PEEP higher than 15 cm H_2O and prolonged prone position are recommended for more severe patients to improve their survival. Adjunctive recruitment maneuvers can be used to improve oxygenation and allow more homogeneous ventilation and PEEP titration. In refractory hypoxemia and especially in younger patients with prognosis, extra-corporeal veno-venous membrane oxygenation support can be used.

Keywords: ARDS, mechanical ventilation, ECMO, hypoxemia

1. Diagnosing and evaluating the severe acute respiratory distress syndrome

Acute respiratory distress syndrome is characterized by an increase of the permeability of the lungs alveolar-capillary membranes leading to the extravasation of the intravascular plasma of the lungs capillary network surrounding the alveoli to the alveolar spaces that were previously filled by air. This accumulation of liquid rich in proteins inside the alveolar spaces turns an air-filled lungs into a heavy high-osmotic pressure liquid-filled lungs and the consequent collapse of the lowermost lung regions, shunt, refractory hypoxemia, decrease in lungs compliance and increase in dead space that are more pronounced the more severe the permeability changes of the pulmonary alveoli-capillary membrane. Regarding the physiopathology of ARDS, the hallmark mechanism of injury is inflammation leading to increased endothelial and epithelial permeability and liberation of receptors for angiotensin-2 and advanced glycation end products (RAGE) [1–4].

2. Severe ARDS according to Berlin definition

According to the recent Berlin definition, severe acute respiratory distress syndrome is defined by bilateral pulmonary infiltrates of recent onset (less than 1 week) in a patient that have a $\text{PaO}_2/\text{FIO}_2$ equal or less than 100 with a positive end-expiratory pressure equal or more 5 cm H_2O with no evidence of cardiac failure or hypervolemia. The patient also needs to present a risk factor for ARDS development as respiratory infection, gastric content aspiration, lungs contusion, blood products transfusion, sepsis, high-risk trauma, high-risk surgery, shock, and pancreatitis [1–4].

3. The hole of extravascular lung water and pulmonary vascular index in the evaluation of severe ARDS

The extravascular lung water index (EVLWi) is calculated as the intra-thoracic total volume minus the intra-thoracic blood volume indexed by predicted body weight measured using a transpulmonary thermodilution method. The pulmonary vascular permeability index (PVPI) was calculated as extravascular lung water divided by the pulmonary blood volume [5]. Theoretically, the greater the EVLWi and PVPi, the greater the severity of ARDS. Recently, Kushimoto and colleagues [5] evaluated the relationship among the severity categories of ARDS as defined by the Berlin definition, EVLWi and PVPi to confirm their predictive validity for severity of ARDS. They measured EVLWi and PVPi in 195 patients with an EVLWi of ≥ 10 mL/kg, which fulfilled the Berlin definition of ARDS in 23 intensive care units for three consecutive days. Patients with moderate and severe ARDS had higher acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment scores (SOFA) on the day of enrollment compared to patients with mild ARDS. Patients with severe

ARDS had higher EVLWi (severe, 19.1; moderate, 17.2; mild, 16.1; $P < 0.05$) and PVPI (3.2; 3.0; 2.7; $P < 0.05$). When the authors evaluated 495 independent measurements over three consecutive days, they observed a moderate and negative correlation between $\text{PaO}_2/\text{FIO}_2$ ratio and EVLWi ($r = -0.355$, $P < 0.001$) and $\text{PaO}_2/\text{FIO}_2$ and PVPi ($r = -0.345$, $P < 0.001$). The authors observed an association between ARDS severity according to Berlin definition and 28-day mortality rate: severe, the odds ratio 4.167 relative to mild.

4. The hole of pulmonary arterial hypertension and right ventricular dysfunction in ARDS severity stratification

Hemodynamic data from the ARDSnet Fluids and Catheter Therapy Trial (FACCT) [6] that analyzed 475 patients randomized to receive a pulmonary artery catheter for ARDS management, none of the baseline measures of cardiopulmonary dysfunction distinguished survivors from nonsurvivors. When the authors measured the transpulmonary gradient (TGP), they observed that 73% of the ARDS patients monitored with the Swan-Ganz had an elevated TGP (>12 mm Hg). Patients with a TGP > 12 mm Hg had a significantly greater mortality rate than patients with a TGP < 12 mm Hg (30 vs. 19%; $P = 0.02$). In multivariate analysis, an elevated TGP and a high PVRi remained an independent predictor of an adverse outcome in this ARDS population. In a recent, prospective and observational study in an academic medical intensive care unit in France [7], 226 consecutive patients with moderate to severe ARDS ventilated who received a protective ventilation (plateau pressure less than 30 cm H_2O and mean PEEP of 8.8 ± 3.6 cm H_2O , underwent transesophageal echocardiography (TEE) within the first 3 days after the diagnosis of ARDS. Cor pulmonale (dilated right ventricle associated with septal dyskinesia), was detected in 49 patients (prevalence of 22%; 95% confidence interval, 16–27%). Patients who had cor pulmonale presented a significantly higher 28-day mortality rate (60 vs. 36%, $P < 0.01$) compared with the ARDS patients without cor pulmonale. Sepsis and higher values of driving pressure were associated with the presence of cor pulmonale that was an independent risk factor for 28-day mortality in their population. Taking these results into consideration, a subgroup of ARDS severity stratification: ARDS with right ventricular dysfunction should be proposed especially because different ventilatory strategies (prone position, low driving pressures, titrated PEEP levels), distinct pharmacologic therapy (pulmonary artery vasodilators) should be tested in order to improve prognosis of this subgroup of ARDS patients [4].

5. The hole of low respiratory system compliance in ARDS severity stratification

Other factors that are associated with severe ARDS are respiratory system compliance of less than 20 mL/cm H_2O , pulmonary dead space fraction greater than 0.60, as well as high APACHE II and SAPS II score as well as multiple organ failures (the higher the organ failures, the higher the patient mortality) [1–4].

Ichikado [8] showed that fibroproliferation signs in high-resolution CT evaluation of early ARDS patients were correlated with higher mortality and ventilator dependency. The lung SAFE study [3], an international, multicenter, prospective cohort study of patients undergoing invasive or noninvasive ventilation, conducted in 459 ICUs from 50 countries across five continents showed that 2,377 out of 29,144 patients developed ARDS in the first 48 h and whose respiratory failure was managed with invasive mechanical ventilation. The period prevalence of mild ARDS was 30.0% (95% CI, 28.2–31.9%); of moderate ARDS, 46.6% (95% CI, 44.5–48.6%); and of severe ARDS, 23.4% (95% CI, 21.7–25.2%). The cumulative frequency distribution of tidal volume was similar in patients in each severity category, with 65% of patients with acute respiratory distress syndrome (ARDS) receiving a tidal volume of 8 mL/kg of predicted body weight or less. In contrast, a right shift of the cumulative frequency distribution curves of plateau pressures was seen for increasing ARDS severity category, with plateau pressure of more than 30 cm H₂O in 8.5% of patients for which these data were available. There was a lower likelihood of survival to day 28 with increasing severity of acute respiratory distress syndrome (ARDS) at day 1. Patients with a driving pressure of greater than 14 cm H₂O on day 1 of ARDS criteria had a higher mortality. Taking into consideration, these data that tidal volume ventilation was similar across the ARDS severity but inspiratory driving pressure less than 14 cm H₂O was associated with decreased mortality of those patients one could argue that in the future tidal volume should be titrated according to the derived driving inspiratory pressure.

Amato and colleagues [9] analyzed individual data from 3562 patients with ARDS enrolled in nine previously published randomized clinical trials of mechanical ventilation using a multilevel mediation analysis. They observed a strong association between driving pressure and ARDS survival even though all the ventilator settings that were used were lung protective (RR of death: 1.36, 95% CI 1.17–1.58, $P < 0.001$). These observations suggest that tidal volume might be adjusted to the resultant airway driving pressure in addition to the adjustment to the predicted body weight. They also observed that airway driving pressures higher than 15 cm H₂O were associated with increasing rates of mortality in ARDS patients. Recently, Villar and colleagues [10] analyzed the data from two observational studies enclosing 778 patients with moderate and severe ARDS. They assessed the risk of hospital death based on quantiles of tidal volume, positive end-expiratory pressure, plateau inspiratory pressure and airway driving pressure evaluated 24 h after ARDS diagnosis while the patients were ventilated with lung protective ventilation. The authors verified that positive end expiratory pressure and tidal volume that were set according to a protective lung ventilation strategy had no impact on mortality while a plateau pressure higher than 29 cm H₂O and a driving pressure higher than 19 cm H₂O were associated with a higher hospital mortality.

As respiratory system driving pressure does not account for variable chest wall compliance or different degrees of intra-abdominal pressures or even more to the presence of inspiratory efforts or asynchrony, esophageal manometry can be used to measure transpulmonary pressure that represents the lungs parenchyma stress during tidal volume ventilation. Recently, Baedorf and colleagues examined the relationships between respiratory system and transpulmonary driving pressure measured at baseline, 5 min and 24 h after PEEP titration and

28-day mortality in 56 ARDS patients. They observed that PEEP titration to target positive end-expiratory transpulmonary pressures resulted in both improved elastance and driving pressures and was associated with improved 28-day mortality.

However, future studies regarding the evaluation of respiratory system and transpulmonary driving pressure in ARDS patients with normal and increased abdominal pressure and various degrees of respiratory system compliance is still needed in order to establish the value of both as a bedside ventilator target as well as a prognosticator of evolution and mortality of those patients.

6. The hole of increased dead space, high PaCO₂ and multiple organ failure in severe ARDS

Increased dead space in the first day of mechanical ventilation, increased PaCO₂ levels with protective ventilation and multiple organ failure are all associated with higher mortality in severe ARDS. However, specific therapeutic aiming to decrease dead space fraction, decrease PaCO₂ levels or even multimodal therapeutic approach to treat multiple organ failure still need to be defined and tested [4].

7. Does the risk factor for ARDS influence the patient mortality rate?

Recently, Villar and colleagues [11] showed in a cohort of 778 patients that severe ARDS occurred in about 37.5% at ARDS diagnosis and after 24 h of ARDS onset 20.8% and moderate to severe ARDS had an overall mortality of 38.8%. They also showed that the underlying cause of ARDS influence in the mortality ratio (the mortality ratio was higher in pancreatitis and progressively lower in sepsis, pneumonia and trauma).

8. Treating the severe ARDS patient

Low-tidal ventilation (≤ 6 mL/kg of predicted body weight) must be initiated as soon as the ARDS patient is intubated and mechanically ventilated. The predicted body weight (PBW) can be calculated as follows: for women, $PBW = 45.5 + 0.91 (\text{height in centimeters} - 152.4)$ and for men, $PBW = 50.0 + 0.91 (\text{height in centimeters} - 152.4)$. It is well documented that lower tidal volumes (6 mL/kg of predicted body weight) compared to higher tidal volumes (12 mL/kg of predicted body weight) associated with PEEP levels titrated by a PEEP/FIO₂ table reduced mortality in a randomized, clinical trial that analyzed 861 ARDS patients (ARMA trial) [12].

It is crucial to adjust tidal volume to lung size that depends of the height and sex, but more importantly is to adjust the tidal volume to functional lung size that depends on the ARDS severity (lung compliance), sex, height, and chest wall compliance. The patient with severe

ARDS and a low compliance will be ventilated with high airway pressures if ventilated with 6 mL/predicted body weight. Amato and colleagues [9], in 2015, reported that driving pressure (ΔP), that can be also be represented by tidal volume (VT)/respiratory system compliance (CRS), in which VT is intrinsically normalized to functional lung size, was a ventilatory variable more strongly associated with survival than VT or PEEP in patients who are not actively breathing. Using a statistical tool known as multilevel mediation analysis to study individual data from 3562 patients with ARDS enrolled in nine previously reported randomized trials, they examined ΔP as an independent variable associated with survival. In the mediation analysis, they estimated the isolated effects of changes in ΔP resulting from randomized ventilator settings while minimizing confounding due to the baseline severity of lung disease. The authors observed that among ventilation variables, ΔP was most strongly associated with survival. A 1-SD increment in ΔP (approximately 7 cm of water) was associated with increased mortality (relative risk, 1.41; 95% confidence interval [CI], 1.31–1.51; $P < 0.001$), even in patients receiving “protective” plateau pressures and VT (relative risk, 1.36; 95% CI, 1.17–1.58; $P < 0.001$). Individual changes in VT or PEEP after randomization were not independently associated with survival; they were associated only if they were among the changes that led to reductions in ΔP (mediation effects of ΔP , $P = 0.004$ and $P = 0.001$, respectively). They concluded that ΔP was the ventilation variable that best stratified risk. Decreases in ΔP owing to changes in ventilator settings were strongly associated with increased survival.

Moreover, recent evidences [13] showed that in severe ARDS patients, inspiratory efforts during assisted ventilation could worsen ventilator lung injury induced by the mechanical ventilation during the ventilatory support of the ARDS patients. This associated and added injury could explain the results of a phase IV randomized controlled trial in moderate-severe ARDS patients ($\text{PaO}_2/\text{FIO}_2 < 150$), comparing cisatracurium to placebo for 48 h showed an improved adjusted 90-day survival rate and increased ventilator-free in the cisatracurium group without a significant increase in muscle weakness. Short-term paralysis may facilitate patient-ventilator synchrony in the setting of lung protective ventilation. Short-term paralysis would eliminate patient triggering and expiratory muscle activity. In combination, these effects may serve to limit regional overdistention and cyclic alveolar collapse. Paralysis may also act to lower metabolism and overall ventilatory demand [14]. Recently, Sottile and colleagues [15] showed that the use of neuromuscular blockade in ARDS patients receiving low tidal volume ventilation and a $\text{PaO}_2/\text{FIO}_2$ ratio less than 120 were associated with decreased biomarkers of epithelial (serum surfactant protein-D) and endothelial (serum Von Willebrand factor) lung injury and systemic inflammation (serum interleukin 8).

At the same time, that an adequate sedation, an adequate short-term paralysis and low tidal volume were set in severe ARDS patients [16], an adequate respiratory rate must be concurrently set in order to keep a minute ventilation around 7–8 L/min and a PaCO_2 around 40–60 mm Hg and a pH above 7.2. In the more severe ARDS patients, sometimes after the adjustment of a minute ventilation around 7–8 L/min with tidal volumes lesser than 6 mL/kg of predicted body weight, the PaCO_2 levels stay above 80 mm Hg and pH less than 7.2 (specially patients with septic shock and metabolic acidosis). In these cases, the VCO_2 must be assessed and be kept as least as possible (fever control, low carbohydrate intake) and hemodialysis can be initiate (especially in ARDS patients with concomitant acute renal failure) in order to help control the

metabolic acidosis. Efforts must be taken to decrease the pulmonary dead space by means of recruitment maneuvers and PEEP titration, tidal volume and respiratory rate adjustments or even the initiation of prone ventilation. In the most difficult cases, tracheal gas insufflation or extracorporeal CO₂ removal or extracorporeal oxygenation should be started in order to keep the protective low tidal volume ventilation [17].

Permissive hypercapnia can carry potential harmful consequences including pulmonary vasoconstriction and pulmonary hypertension, proarrhythmic effects of increased discharge of catecholamines and cerebral vasodilation yielding increased intracranial pressure. When applying protective ventilation in patients with severe ARDS, special attention should be given to patients with pulmonary hypertension and right ventricular dysfunction that could not tolerate high PaCO₂ and low pH levels. Nonetheless, permissive hypercapnia should probably be used with caution in patients with heart disease and is relatively contraindicated in those with elevated intracranial pressure. In ARDS cases with pulmonary hypertension and right ventricular dysfunction, prone position ventilation should be preferred [17].

Recently, three large clinical trials [18–20], including acute lung injury/ARDS patients ventilated with low tidal-volume, have compared different PEEP strategies (high vs. low), but none of them could show a significant difference in mortality. Moreover, a recent meta-analysis [21] has pooled those trials, revealing some combined benefits of the high PEEP strategy; still, the survival benefit was modest and limited to the subgroup of ARDS patients with PaO₂/FIO₂ < 200 (moderate and severe ARDS according to Berlin definition). Conceptually, one could argue that none of the “high-PEEP” strategies was designed to test the “open-lung hypothesis” postulated by Lachmann, that is, the hypothesis that most of the collapsed lung tissue observed in early ARDS can be reversed at an acceptable clinical cost, potentially resulting in better lung protection [22–24]. According to a recent study by Borges and colleagues [25], a straight test of the “open-lung hypothesis” would certainly require more aggressive recruiting maneuvers in association with individualized, decremental PEEP titration. Recently, de Matos and colleagues [26] reported the experience with maximal recruitment strategy (MRS) in 51 patients with ARDS. MRS consisted of 2-min steps of pressure-controlled ventilation, fixed driving pressure of 15 cm H₂O, respiratory rate of 10 breaths/min, inspiratory/expiratory ratio of 1:1, and stepwise increments in PEEP levels from 10 to 45 cm H₂O (recruitment phase). After that, PEEP was decreased to 25 cm H₂O and, then, from 25 to 10 cm H₂O (PEEP titration phase) in steps of 5 cm H₂O, each one lasting 4 min monitored by thoracic tomography images. At each of the steps, computer tomography image sequences from the carina to the diaphragm were acquired during an expiratory pause of 6–10 s. Visual inspection of the images was performed during the tomographic examination in order to assess the lung collapse in the lungs bases for immediate clinical decision, and after an offline quantitative analysis was realized. Non-aerated parenchyma decreased significantly from 53.6% (interquartile range (IQR): 42.5–62.4) to 12.7% (IQR: 4.9–24.2) ($P < 0.0001$) after MRS. The opening plateau pressure observed during the recruitment protocol was 59.6 (±5.9 cm H₂O), and the mean PEEP titrated after MRS was 24.6 (±2.9 cm H₂O). The mean PaO₂/FiO₂ ratio increased from 125 (±43) to 300 (±103; $P < 0.0001$) after MRS and was sustained above 300 throughout 7 days. MRS showed a statistically significant decrease in non-aerated areas of the ARDS lungs that was accompanied by a significant increment in oxygenation. The potentially recruitable

lung was estimated at 45% (IQR: 25–53). ICU mortality was 28% and hospital mortality was 32%. The independent risk factors associated with mortality were older age and higher driving pressures. There were no significant clinical complications with MRS or barotrauma. A better evolution of these ARDS patients with less necessity of oxygen supplementation in the recovery phase of the disease and a better quality of life were observed in these patients [26].

A recent systematic review and meta-analysis [27] that analyzed the effects of recruitment maneuvers for adult patients with acute respiratory distress syndrome showed an overall pool effect of a significant decrease on mortality in these patients and no associated increase in barotrauma. However, soon after, a large prospective, multicenter and controlled trial (ART trial) [28] that compared recruitment maneuver and best-compliance PEEP titration in 501 ARDS patients with 509 ARDS patients ventilated with low PEEP showed an increased 6-month mortality in both groups, but higher in the recruitment and PEEP titration group (65.3 vs. 59.9%, respectively, $P = 0.04$). However, in our opinion, the recruitment maneuver tested in ART trial was abrupt and short (started at 25 cm H₂O PEEP, duration of 1 s and not imaging monitored) what could have contributed to the higher levels of observed barotrauma and mortality [29]. When we combined the results of the systematic review and meta-analysis with the ART results, we observed a total of 1144 patients undergoing recruitment maneuvers and PEEP titration and 1179 controls with standard ventilation with a final result of no significant differences in mortality relative risk of 0.91 [95% CI, 0.74–1.13]. The most effective recruitment maneuver and PEEP titration in ARDS remain to be determined [29].

Our group is used to apply maximal recruitment strategy maneuvers in our severe ARDS patients with PEEP titration with thoracic tomography with good results. Here, we present a case of a 47-year-old man, previously asymptomatic, that started with cough, dyspnea, and an acute hypoxemic respiratory failure. The chest-X-ray showed a bilateral pulmonary infiltrate that predominates in the lower lungs fields (**Figure 1**). SpO₂ in ambient air was 77% and after oxygen mask of 100% SpO₂ was 88% and he needed intubation and mechanical ventilation. Arterial pressure is of 11 × 7 cm Hg and HR of 110 rpm. Hemocultures and tracheal secretion were collected as well as a nasopharyngeal swab for respiratory viruses. Oseltamivir, clarithromycin and ceftriaxone were initiated. A transthoracic echocardiogram showed normal right and left ventricular function and a normal arterial pulmonary pressure. A protective mechanical ventilation was initiated with tidal volume of 6 mL/kg/predicted body weight (420 mL), RR of 20 rpm, PEEP of 15 cm H₂O, FIO₂ of 100%, SpO₂ de 90% and an arterial blood gas analysis showed a pH of 7,35, PaCO₂ of 50 mm Hg, PaO₂ of 60 mm Hg, sodium bicarbonate of 23 and base excess of -1, lactate of 10 mg/dL, SvO₂ of 70 mm Hg, Hb of 13 g/dL, 12,000 leucocytes, platelets of 250,000, reactive C-protein of 120 mg/L, BNP of 40 pg/mL. He was submitted to maximal recruitment strategy maneuvers and PEEP titration of 25 cm H₂O in the tomography room (**Figure 2**). The PaO₂/FIO₂ ratio increased from 60 to 200, and after 3 days, he was with PEEP of 15 cm H₂O and a PaO₂/FIO₂ of 300. After 10 days, he was extubated and presented in ambient air a SpO₂ of 95% and an expressive improvement in chest X-ray (**Figure 3**). All the collect cultures and the nasopharyngeal swab for respiratory viruses were negative. The thoracic tomography performed 3 days after extubation showed an important improvement of the lungs infiltrates (**Figure 4**).

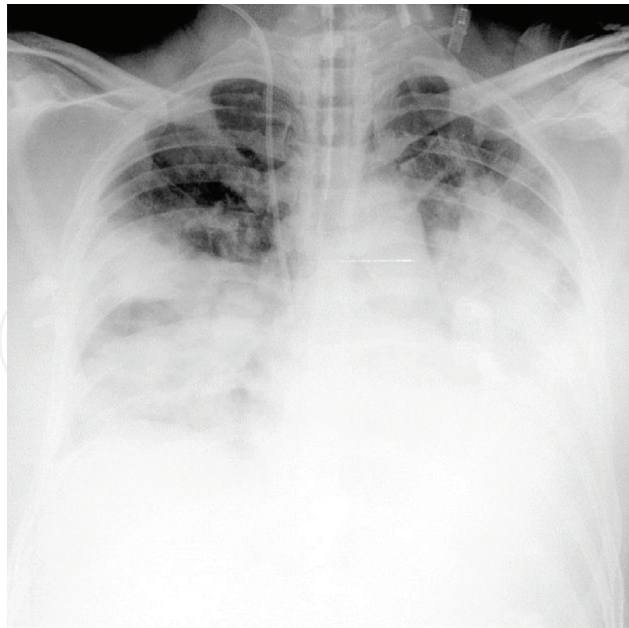


Figure 1. Chest X-ray showing bilateral pulmonary infiltrates that predominate in lower lungs fields.

Recent evidence showed that prolonged prone position ventilation (16 h) must be used in early ARDS with $\text{PaO}_2/\text{FIO}_2 < 150$ with PEEP levels of or more than 5 cm H_2O in order to significantly improved 90-day mortality compared to supine ventilation (PROSEVA trial) [30].

Recent meta-analysis also showed that in the era of low tidal ventilation, the prone position use improved mortality of moderate/severe ARDS patients that needed invasive mechanical ventilatory support [31]. If PEEP titration during prone position, ventilation should improve survival of ARDS patients, which is still a matter of debate.

For patients in whom gas exchange is refractory to conventional ventilation and other advanced therapies, extracorporeal membrane oxygenation (ECMO) may be appropriate as salvage therapy. Venovenous ECMO may be able to support refractory hypoxemia in the setting of severe ARDS. It may also be used for carbon dioxide removal when respiratory system compliance is severely compromised and efforts to maintain plateau airway pressures within acceptable parameters lead to unsustainable levels of hypercapnia and respiratory acidosis.

Prospective randomized controlled trial of ECMO in severe ARDS, reported in 2009, was the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial [32], in which 180 subjects with severe ARDS were randomized to conventional mechanical ventilation or referral to a specialized center for consideration of ECMO. The United Kingdom randomized and prospective clinical trial (CESAR) revealed a survival advantage in the ECMO group; the ECMO group had a 63% survival after 6 months, while the control group had a 47% survival rate. The study was criticized because there was no standardized protocol management for the control group and some patients in the ECMO group did not receive the proposed treatment. The authors demonstrated that this strategy is also likely to be cost-effective in settings with similar services to those in the United Kingdom. Patients should be considered for weaning

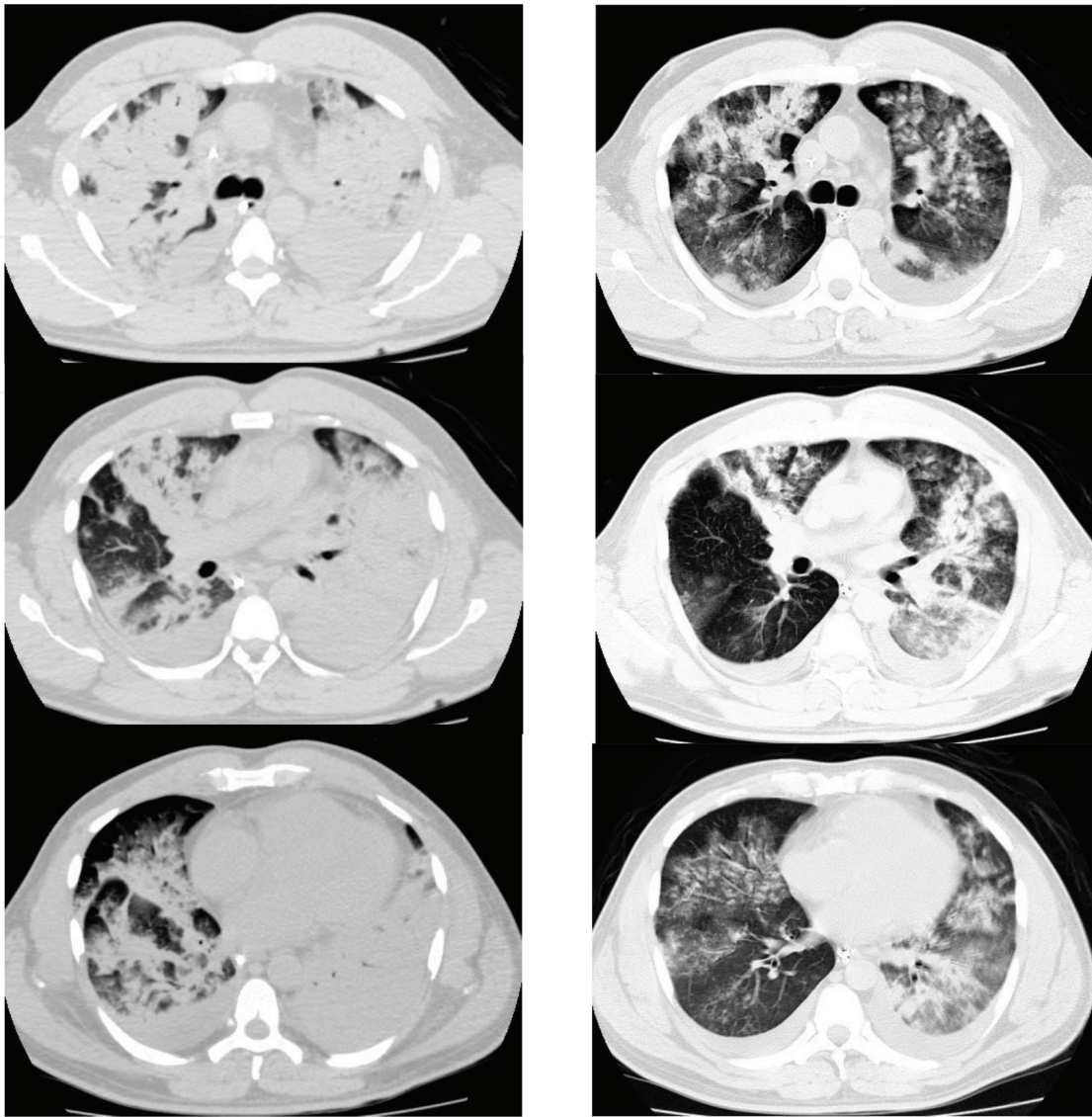


Figure 2. Thoracic tomography before and after maximal recruitment maneuvers and PEEP titration. Pre-recruitment PEEP of 10 cm H₂O. Pos-recruitment PEEP of 25 cm H₂O.



Figure 3. Chest-X-ray day 1, day 3, and day 10 after admission (day of extubation).

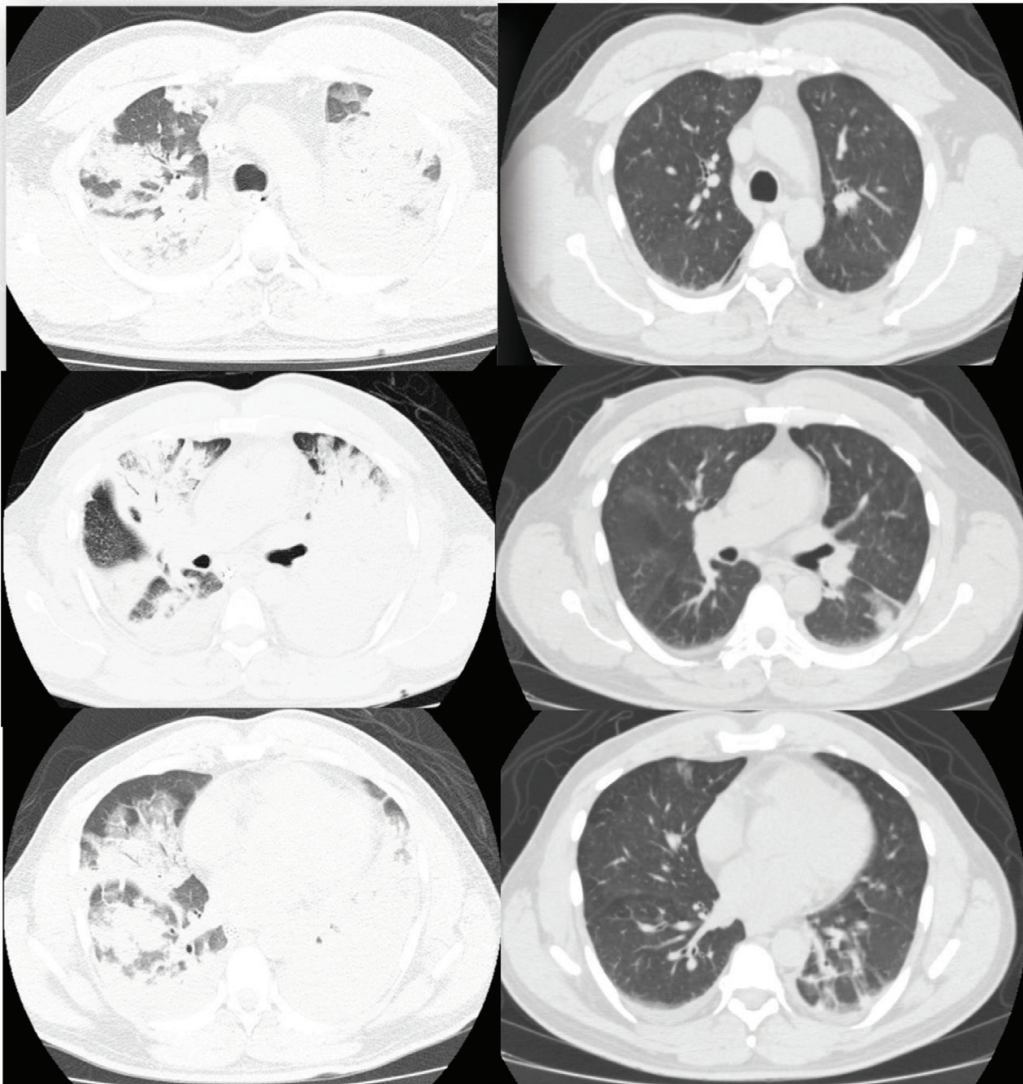


Figure 4. Thoracic tomography at first day after admission and thoracic tomography 3 days after extubation.

from venovenous ECMO once the underlying disease process for which ECMO was initiated has sufficiently resolved so that they can be safely and adequately supported by protective ventilatory strategy and oxygenation support without evidence of excessive respiratory work of breathing. Markers of sufficient native lung function recovery include adequate gas exchange reserve, acceptable respiratory system compliance, and improvement in chest images [32].

Another recent approach for application of extracorporeal carbon dioxide removal new devices (ECMO-R) in ARDS patients is the observation in thoracic tomography of ARDS patients that in severe ARDS, even the low tidal volume ventilation with 6 mL/kg of predicted body weight can cause tidal hyperdistension in the nondependent regions of the lungs accompanied by plateau airway pressures greater than 28 cm H₂O and elevated plasma markers of inflammation. Application of ECMO-R in these severe ARDS patients could allow the authors to decrease the tidal volume to less than 6 mL/kg with a consequent plateau pressure less than 25 cm H₂O that was associated with lower levels of lung-derived inflammatory cytokines and a lower radiographic

index of lung injury [33], but prognostic implications of ECMO-R devices application in clinical practice are still under investigation [34]. Pumpless interventional lung assist (iLA) is also used in patients with ARDS and is aimed at improving extracorporeal gas exchange with a membrane integrated in a passive arteriovenous shunt. iLA can be used in severe ARDS patients as an extracorporeal device to remove CO₂ enabling low tidal volume and a reduced inspiratory plateau pressure in the mechanical ventilator in extremely severe ARDS patients. iLA device was used in 51 severe ARDS patients by Zimmermann and colleagues with a decrease in PaCO₂ allowing the ultraprotective ventilation (lower tidal volume and plateau inspiratory pressures) with a hospital mortality of 49% [35]. More recently, the use of an ultraprotective strategy using 4 mL/kg of predicted body weight associated with low flow extracorporeal carbon removal in 15 moderate ARDS patients was described by Faneli and coworkers [36]. Additional data to the use of ECMO in ARDS patients will be added with the publication of EOLIA trial (ClinicalTrials.gov Identifier: NCT01470703), a prospective and randomized trial that evaluated the role of ECMO in severe ARDS that has finished but not published yet.

In conclusion, the severe ARDS is defined as an acute bilateral pulmonary infiltrate onset, in a patient with a PaO₂/FIO₂ equal or less than 100 with a positive end expiratory pressure equal or more than 5 cm H₂O that have an ARDS risk factor with no signs of cardiac failure or hypervolemia. Thus, when an intensivist evaluates an ARDS patient severity, he/her has to take into consideration the patient's age, cause of ARDS, the PaO₂/FIO₂ ratio, response to PEEP, prone position, PaCO₂ with protective ventilation (6 mL/predicted body weight), right ventricular function and level of pulmonary artery pressure, presence of shock (and necessity of vasoactive drugs), APACHE II score, number of organ failures (specially renal failure). The severe ARDS patients present a higher mortality ratio and required an extremely careful and specialized treatment. The cause of ARDS initiation should be addressed and promptly treated. These patients present a more difficult mechanical ventilatory support (higher airway pressures with low tidal ventilation and higher PaCO₂ levels). They should be adequately monitored (airway and esophageal pressure measurements, bedside echocardiography and lung ultrasound, if possible). Protective ventilatory strategy must be offered and monitored (low tidal volume (less than 6 mL/kg of predicted body weight) and low distending inspiratory driving pressures (less than 15 cm H₂O) with adequate PEEP levels, and early prone position applied for more than 16 h. The possible benefits for adjunctive ventilatory support therapy (higher PEEP, recruitment maneuvers, inhaled nitric oxide, ECMO and continuous hemodialysis) in the refractory cases should be offered, observing and monitoring the cross-talking among the multiple organ dysfunctions and guiding and changing the treatment according to the patients' responses. The more difficult cases must be treated in specialized centers with expertise supervision [4, 17, 26, 37, 38].

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References

- [1] Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: The Berlin definition. ARDS definition task force. *JAMA*. 2012;**307**(23):2526-2533
- [2] Caser EB, Zandonade E, Pereira E, Gama AM, Barbas CS. Impact of distinct definitions of acute lung injury on its incidence and outcomes in Brazilian ICUs: prospective evaluation of 7,133 patients. *Critical Care Medicine*. 2014;**42**(3):574-582
- [3] Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A, LUNG SAFE investigators; ESICM trials group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;**315**(8):788-800
- [4] Barbas CS, Isola AM, Caser EB. What is the future of acute respiratory distress syndrome after the Berlin definition? *Current Opinion in Critical Care*. 2014;**20**(1):10-16
- [5] Kushimoto S, Endo T, Yamanouchi S, Sakamoto T, Ishikura H, Kitazawa Y, Taira Y, Okuchi K, Tagami T, Watanabe A, Yamaguchi J, Yoshikawa K, Sugita M, Kase Y, Kanemura T, Takahashi H, Kuroki Y, Izumino H, Rinka H, Seo R, Takatori M, Kaneko T, Nakamura T, Irahara T, Saito N. The Picco Pulmonary Edema Study Group. Relationship between extravascular lung water and severity categories of acute respiratory distress syndrome by the Berlin definition. *Critical Care*. 2013;**17**(4):R132
- [6] Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *New England Journal of Medicine*. 2006;**354**(24):2564-2575
- [7] Boissier F, Katsahian S, Razazi K, Thille AW, Roche-Campo F, Leon R, Vivier E, Brochard L, Vieillard-Baron A, Brun-Buisson C, Mekontso Dessap A. Prevalence and prognosis of cor pulmonale during protective ventilation for acute respiratory distress syndrome. *Intensive Care Medicine*. 2013;**39**(10):1725-1733
- [8] Ichikado K. The Berlin definition and clinical significance of high resolution CT (HRCT) imaging in acute respiratory distress syndrome. *Masui*. 2013;**62**(5):522-531
- [9] Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, Richard JC, Carvalho CR, Brower RG. Driving pressure and survival in the acute respiratory distress syndrome. *The New England Journal of Medicine*. 2015;**372**(8):747-755
- [10] Villar J, Martín-Rodríguez C, Domínguez-Berrot AM, Fernández L, Ferrando C, Soler JA, Díaz-Lamas AM, González-Higueras E, Nogales L, Ambrós A, Carriedo D, Hernández M, Martínez D, Blanco J, Belda J, Parrilla D, Suárez-Sipmann F, Tarancón C, Mora-Ordoñez JM, Blanch L, Pérez-Méndez L, Fernández RL, Kacmarek RM. Spanish initiative for epidemiology, stratification and therapies for ARDS (SIESTA) investigators network. A quantile analysis of plateau and driving pressures: Effects on mortality in patients with acute respiratory distress syndrome receiving lung-protective ventilation. *Critical Care Medicine*. 2017;**45**(5):843-850

- [11] Villar J, Martínez D, Mosteiro F, Ambrós A, Añón JM, Ferrando C, Soler JA, Montiel R, Vidal A, Conesa-Cayuela LA, Blanco J, Arrojo R, Solano R, Capilla L, Del Campo R, Civantos B, Fernández MM, Aldecoa C, Parra L, Gutiérrez A, Martínez-Jiménez C, González-Martín JM, Fernández RL, Kacmarek RM. Stratification and outcome of acute respiratory distress syndrome (STANDARDS) network. Is overall mortality the right composite endpoint in clinical trials of acute respiratory distress syndrome? *Critical Care Medicine*. Feb 7, 2018. DOI: 10.1097/CCM.0000000000003022. [Epub ahead of print]
- [12] The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *The New England Journal of Medicine*. 2000;**342**:1301-1308
- [13] Yoshida T, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa EL, Tucci MR, Zin WA, Kavanagh BP, Amato MB. Spontaneous effort causes occult pendelluft during mechanical ventilation. *American Journal of Respiratory and Critical Care Medicine*. 2013;**188** (12):1420-1427
- [14] Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *The New England Journal of Medicine*. 2010;**363**(12):1107-1116
- [15] Sottile PD, Albers D, Moss MM. Neuromuscular blockade is associated with the attenuation of biomarkers of epithelial and endothelial injury in patients with moderate-to-severe acute respiratory distress syndrome. *Critical Care*. 2018;**22**:63
- [16] Barbas CSV. In: Chiumello D, editor. *Acute Respiratory Distress Syndrome (ARDS)*. Switzerland: Springer International Publishing; 2017. pp. 29-39
- [17] Barbas CS, Matos GF, Amato MB, Carvalho CR. Goal-oriented respiratory management for critically ill patients with acute respiratory distress syndrome. *Critical Care Research and Practice*. 2012;**2012**:952168
- [18] Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *The New England Journal of Medicine*. 2004;**351**:327-336
- [19] Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L. Expiratory pressure (express) study group. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA*. 2008;**299**:646-655
- [20] Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE. Lung open ventilation study investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA*. 2008;**299**:637-645

- [21] Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt G. Higher vs. lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: Systematic review and meta-analysis. *JAMA*. 2010;**303**:865-873
- [22] Lachmann B. Open up the lung and keep the lung open. *Intensive Care Medicine*. 1992;**18**:319-321
- [23] Barbas CS, de Matos GF, Pincelli MP, da Rosa Borges E, Antunes T, de Barros JM, Okamoto V, Borges JB, Amato MB, de Carvalho CR. Mechanical ventilation in acute respiratory failure: Recruitment and high positive end-expiratory pressure are necessary. *Current Opinion in Critical Care*. 2005;**11**:18-28
- [24] Papadakos PJ, Lachmann B. The open lung concept of mechanical ventilation: The role of recruitment and stabilization. *Critical Care Clinics*. 2007;**23**:241-250
- [25] Borges JB, Okamoto VN, Matos GF, Caramez MP, Arantes PR, Barros F, Souza CE, Victorino JA, Kacmarek RM, Barbas CS, Carvalho CR, Amato MB. Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*. 2006;**174**:268-278
- [26] de Matos GF, Stanzani F, Passos RH, Fontana MF, Albaladejo R, Caserta RE, Santos DC, Borges JB, Amato MB, Barbas CS. How large is the lung recruitability in early acute respiratory distress syndrome: A prospective case series of patients monitored by computed tomography. *Critical Care*. 2012;**16**(1):R4
- [27] Goligher EC, Hodgson CL, Adhikari NKJ, Meade MO, Wunsch H, Uleryk E, Gajic O, Amato MPB, Ferguson ND, Rubenfeld GD, Fan E. Lung recruitment maneuvers for adult patients with acute respiratory distress syndrome. A systematic review and meta-analysis. *Annals of the American Thoracic Society*. 2017;**14**(4):S304-S311
- [28] Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, Cavalcanti AB, Suzumura ÉA, Laranjeira LN, Paisani DM, Damiani LP, Guimarães HP, Romano ER, Regenga MM, Taniguchi LNT, Teixeira C, Pinheiro de Oliveira R, Machado FR, Diaz-Quijano FA, Filho MSA, Maia IS, Caser EB, Filho WO, Borges MC, Martins PA, Matsui M, Ospina-Tascón GA, Giancursi TS, Giraldo-Ramirez ND, Vieira SRR, Assef MDGPL, Hasan MS, Szczeklik W, Rios F, Amato MBP, Berwanger O, Ribeiro de Carvalho CR. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs. low PEEP on mortality in patients with acute respiratory distress syndrome: A randomized clinical trial. *Journal of the American Medical Association*. 2017;**318**(14):1335-1345
- [29] Barbas CSV, Nemer SN. Lung recruitment and positive end-expiratory pressure titration in patients with acute respiratory distress syndrome. *Journal of the American Medical Association*. 2018;**319**(9):933
- [30] Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M,

- Hilbert G, Bengler C, Richecoeur J, Gainnier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L. PROSEVA study group. Prone positioning in severe acute respiratory distress syndrome. *The New England Journal of Medicine*. 2013;**368**(23):2159-2168
- [31] Beitler JR, Shaefi S, Montesi SB, Devlin A, Loring SH, Talmor D, Malhotra A. Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: A meta-analysis. *Intensive Care Medicine*. 2014;**40**(3):332-341
- [32] Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. *The Lancet*. 2009;**374**(9698):1351-1363
- [33] Ranieri VM, Terragni PP, Del Sorbo L, et al. Tidal volume lower than 6 ml/kg enhances lung protection: Role of extracorporeal carbon dioxide removal. *Anesthesiology*. 2009;**111**(4):826-835
- [34] Costa EL, Amato MB. Ultra-protective tidal volume: How low should we go? *Critical Care*. 2013;**17**(2):127
- [35] Zimmermann M, Bein T, Arlt M, et al. Pumpless extracorporeal interventional lung assist in patients with acute respiratory distress syndrome: A prospective pilot study. *Critical Care*. 2009;**13**(1):2009, R10
- [36] Fanelli V, Ranieri MV, Mancebo J, Moerer O, Quintel M, Morley S, Moran I, Parrilla F, Costamagna A, Gaudiosi M, Combes A. Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome. *Critical Care*. 2016;**20**(1):36
- [37] Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: Advances in diagnosis and treatment. *JAMA*. 2018;**319**(7):698-710
- [38] Gattinoni L, Marini JJ, Quintel M. Time to rethink the approach to treating acute respiratory distress syndrome. *Journal of the American Medical Association*. 2018;**319**(7):664-666